Future cardiometabolic implications of insulin hypersecretion in response to oral glucose: a prospective cohort study

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Summary

Background The cardiometabolic implications of postprandial hyperinsulinemia are unclear with recent studies suggesting both adverse and beneficial associations. We aimed to evaluate the longitudinal cardiometabolic implications of the post–challenge insulin secretory response over 4-years follow-up.

Methods In this prospective cohort study, conducted in Toronto (Ontario, Canada), women comprising the full range of antepartum glucose tolerance were recruited in pregnancy (at the time of glucose tolerance screening, late in the second trimester) to undergo cardiometabolic testing in the years thereafter. Participants underwent oral glucose tolerance tests (OGTT) at 1-year, 3-years, and 5-years postpartum, enabling serial assessment of cardiovascular risk factors, glucose tolerance, insulin sensitivity or resistance (Matsuda index, HOMA-IR), and beta-cell function—via Insulin Secretion-Sensitivity Index-2 (ISSI-2) and insulinogenic index/HOMA-IR (IGI/HOMA-IR). Baseline post–challenge insulinemia was assessed with the corrected insulin response (CIR) at 1-year. Cardiometabolic factors were compared between baseline CIR tertiles.

Findings Between Oct 23, 2003 and March 31, 2014, 306 women were enrolled. In this study population, there was progressive worsening of waist circumference ($p = 0.016$), HDL ($p = 0.018$), CRP ($p = 0.006$), and insulin sensitivity ($p < 0.001$) from the lowest to middle to highest tertile of CIR at 1-year. However, these adverse features were accompanied by progressively better beta-cell function (both $p < 0.001$), coupled with lower fasting and 2-h glucose on the OGTT (both $p < 0.001$). On adjusted longitudinal analyses, higher CIR tertile at 1-year was independently associated with (i) higher ISSI-2 and IGI/HOMA-IR and (ii) lower fasting and 2-h glucose at both 3-years and 5-years (all $p < 0.001$), but was not associated with BMI, waist, lipids, CRP or insulin sensitivity/resistance. The highest CIR tertile at 1-year predicted lower risk of pre-diabetes or diabetes at both 3-years (adjusted OR = 0.19; 95% CI 0.08–0.45) and 5-years (aOR = 0.18; 0.08–0.39), relative to the lowest tertile.

Interpretation A robust post–challenge insulin secretory response does not indicate adverse cardiometabolic health but, rather, portends favourable metabolic function in the years to come. Future long-term study of the implications of the post–challenge insulinemic response is warranted.

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Keywords: Postprandial hyperinsulinemia; Beta-cell function; Insulin resistance; Pre-diabetes

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Twitter Summary: A brisk post–challenge insulin secretory response portends favourable metabolic function and lower risk of pre-diabetes/diabetes in the years to come. @sinaihealth @UofTmedicine.

Research in context

Evidence before this study

There currently exists considerable debate about the interpretation of postprandial hyperinsulinemia, with previous studies reporting associations with both adverse and beneficial cardiometabolic features. Indeed, the physiologic relevance and interpretation of postprandial hyperinsulinemia stands at the crux of current debates on the respective etiologies of both obesity and diabetes. Moreover, practitioners who believe that postprandial hyperinsulinemia is metabolically deleterious make clinical recommendations that seek to limit insulinemic excursion after meals. To assess the literature to date, we searched PubMed for studies evaluating postprandial insulin that were published between Jan 1, 1950, and July 1, 2023. This search showed several factors contributing to the conflicted literature, including (i) inconsistent consideration of ambient glycaemia, (ii) cross-sectional analyses, and (iii) a relative paucity of longitudinal studies in which the future cardiometabolic implications of glucose-corrected post–challenge insulinemia have been evaluated. We aimed to evaluate the longitudinal cardiometabolic implications of the glucose-corrected post–challenge insulin secretory response over 4-years of follow-up in a cohort of women reflecting a broad range of future risk of T2DM.

Added value of this study

This prospective, 4-year longitudinal cohort study shows that, on unadjusted cross-sectional analyses, higher glucose-corrected post–challenge insulinemia (measured by the corrected insulin response (CIR)) has associations with both adverse and favourable cardiometabolic features. However, adjusted longitudinal analyses reveal only beneficial future implications, with higher baseline CIR independently associated with better beta-cell function and lower glycaemia at both 2-years and 4-years thereafter. Moreover, higher CIR at baseline is a significant independent predictor of lower future risk of pre-diabetes or diabetes. It thus emerges that a robust post–challenge insulin secretory response does not indicate adverse cardiometabolic health but, rather, predicts favourable metabolic function in the years to come.

Implications of all the available evidence

These data suggest that post–challenge insulinemia does not hold adverse cardiometabolic implications and hence do not support clinical recommendations that focus on limiting the postprandial insulin secretory response for purported metabolic benefit. Future long-term study of the implications of the post–challenge insulinemic response is warranted to confirm such findings.

Introduction

Fasting hyperinsulinemia is generally recognised as a marker of insulin resistance. By contrast, the interpretation of postprandial hyperinsulinemia is less clear and has been the subject of recent debate.[1–8] While postprandial insulin secretion is a physiologic response that is essential for the maintenance of glucose homeostasis, the question that has been raised is whether a brisk hyperinsulinemic response could have adverse cardiometabolic consequences. Indeed, proponents of the carbohydrate-insulin model of obesity have suggested that postprandial hyperinsulinemia following carbohydrate intake induces an anabolic state that contributes to weight gain and the development of insulin resistance.[5,8] In 2018, a Mendelian randomisation study reported that the serum insulin concentration at 30-min after an oral glucose challenge was associated with BMI, consistent with this model.[9] Conversely, in 2022, Nguyen and colleagues[10] noted that, for the assessment of insulin hypersecretion, the serum insulin concentration should account for ambient glycemia and argued that a more appropriate measure is the corrected insulin response (CIR), which was specifically derived for this purpose in 1976[11] and evaluates insulin secretion at 30-min post–challenge in relation to glucose at 30-min.[11–13] In their Mendelian randomisation study,[10] Nguyen et al. noted that higher CIR did not correlate with cardiometabolic disease, in that it was potentially associated with higher BMI but coupled with favourable fat distribution, lower triglycerides and lower likelihood of type 2 diabetes (T2DM).

In the context of these conflicting cross-sectional analyses, the authors noted that a limitation of this literature is a relative paucity of longitudinal studies in which the future cardiometabolic implications of glucose-corrected post–challenge insulinemia have been evaluated, particularly early in the natural history of T2DM.[10]

Our objective in the current study was to evaluate the longitudinal cardiometabolic implications of the glucose-corrected post–challenge insulin secretory response over 4-years of follow-up in a cohort of women reflecting a broad range of future risk of T2DM.

Methods

Study design

We conducted a prospective cohort study in which women comprising the full range of antepartum glucose tolerance were recruited in pregnancy to undergo cardiometabolic testing in the years thereafter. The concept underlying this cohort is that the spectrum of glucose tolerance in pregnancy (from normal glucose tolerance to gestational diabetes [GDM]) identifies women with a broad range of future risk of T2DM and cardiovascular disease,[14–17] such that longitudinal assessment of this

study population can provide insight into the early natural history of these conditions. The study protocol has been described in detail previously.[18,19]

In brief, healthy pregnant adult women were recruited from obstetrics clinics and the ambulatory laboratory at an academic hospital in Toronto, Canada, at the time of glucose tolerance screening late in the second trimester to participate in this study. After pregnancy, participants were assessed at 3-months, 1-year, 3-years and 5-years postpartum, with each visit consisting of a 2-h 75 g oral glucose tolerance test (OGTT), anthropometry, and measurement of traditional and non-traditional cardiovascular risk factors, including lipid profile and C-reactive protein (CRP).

The study protocol has been approved by the Mount Sinai Hospital Research Ethics Board (01-0318-E) and all women provided written informed consent for participation. For the current analysis, CIR at 1-year was evaluated in relation to cardiometabolic risk factors at 1-year, 3-years and 5-years.

Serial cardiometabolic characterisation at study visits

Participants fasted overnight before attending study visits the next morning at the clinical investigation unit at 1-year, 3-years and 5-years postpartum, respectively. As previously described,[18,19] at each OGTT, venous blood samples were drawn for measurement of glucose and specific insulin at fasting and at 30-, 60-, and 120-min post–challenge. Specific insulin was measured with the Roche-Elecsys-1010 immunoassay analyser and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, Canada). Whole-body insulin sensitivity was assessed with the Matsuda index[20] and insulin resistance was assessed by Homeostasis Model Assessment (HOMA-IR).[21] Beta-cell compensation was assessed with Insulin Secretion-Sensitivity Index-2 (ISSI-2), which is an OGTT-based measure that is analogous to the disposition index obtained from the intravenous glucose tolerance test (ivGTT) against which it has been directly validated.[22–24] ISSI-2 exhibits stronger correlation with the disposition index from the ivGTT than do other OGTT-derived measures of beta-cell function (including the Homeostasis Model of Assessment)[23] and has been widely used to measure beta-cell compensation in previous clinical trials and observational studies.[18,19,25–28] A second measure of beta-cell compensation was provided by the insulinogenic index/HOMA-IR.[19] The formulae for all 4 indices are provided in Online Table 1. Glucose tolerance status was determined from the fasting and 2-h glucose measurements on the OGTT as per Diabetes Canada Clinical Practice Guidelines.[29] Pre-diabetes refers to impaired fasting glucose tolerance (IFG) (defined as fasting glucose between 6.1 and 6.9 mmol/l inclusive), impaired glucose tolerance (IGT) (defined as 2-h glucose between 7.8 and 11.0 mmol/l inclusive) or combined IFG and IGT.[29] Total cholesterol, HDL cholesterol, and triglyceride were measured from fasting serum with the Roche Cobas 6000 c 501 analyser (Roche Diagnostics, Laval, Canada). Lipid measurements were standardised by the Centers for Disease Control and Prevention Lipid Standardization Program (Atlanta, GA). LDL cholesterol was determined by Friedewald formula. High-sensitivity CRP (N high-sensitivity CRP reagent) was measured with the Siemens Healthcare Diagnostics BN ProSpec (Siemens Healthcare Diagnostics, Mississauga, Canada). At each study visit, participants also underwent physical examination, including measurement of weight and waist circumference, and completed questionnaires. Physical activity in the preceding year was assessed by Baecke questionnaire[30,31] at each of 1-year, 3-years and 5-years.

Assessment of corrected insulin response (CIR)

Baseline CIR was calculated from insulin and glucose measurements on the OGTT at 1-year, with formula as follows: $CIR = 100 \times \text{insulin}_{30\text{-mins}}/[\text{glucose}_{30\text{-mins}} \times (\text{glucose}_{30\text{-mins}} - 70)]$, where $\text{insulin}_{30\text{-mins}}$ is the insulin value at 30-mins (in μU/mL) and $\text{glucose}_{30\text{-mins}}$ is the glucose value at 30-min (in mg/dL).[10–13] CIR at 1-year served as the exposure variable of interest for the current analysis. The cross–sectional correlations of CIR at 1-year with the indices of insulin sensitivity (Matsuda), insulin resistance (HOMA-IR), and beta-cell compensation (ISSI-2, IGI/HOMA-IR) are provided in Online Table 1.

Statistical analysis

Continuous variables were tested for normality of distribution, and natural log transformations of skewed variables were used, where necessary, in subsequent analyses. The study population was stratified into tertiles based on CIR at 1-year postpartum. Univariate differences across the groups were assessed with analysis of variance or Kruskal–Wallis test for continuous variables and Chi-squared test for categorical variables (Table 1). Mean adjusted levels of cardiometabolic risk factors were obtained from multiple linear regression models and compared between the three tertiles, after adjustment for age, ethnicity, family history of diabetes, parity, baseline BMI at 1-year, duration of breastfeeding, and months since delivery (Fig. 1). The adjusted mean values were calculated according to the model predictions weighted by cell frequencies from the reference grid comprising all factor combinations. Sensitivity analyses were performed with further adjustment for history of GDM. Multiple linear regression analyses were performed to evaluate CIR tertiles at 1-year as predictors of cardiometabolic risk factors at 3-years and 5-years, respectively, after adjustment for clinical risk factors for diabetes (age, ethnicity, family history of diabetes, BMI at 1-year), and baseline (1-year) measure of the respective risk factor (Table 2). Sensitivity analyses were also

	Lowest CIR tertile (0.01–0.30) (n = 102)	Middle CIR tertile (0.30–0.56) (n = 102)	Highest CIR tertile (0.56–10.95) (n = 102)	p
At 1-year				
Age (years)	36.6 (4.8)	36.9 (3.9)	36.1 (4.2)	0.40
Ethnicity:				0.17
White n (%)	77 (75)	70 (69)	72 (71)	
Asian n (%)	16 (16)	21 (21)	12 (12)	
Other n (%)	9 (9)	11 (11)	18 (18)	
Family history of DM n (%)	62 (61)	63 (62)	65 (64)	0.91
Parity:				0.68
One n (%)	55 (54)	51 (50)	47 (46)	
Two n (%)	39 (38)	39 (38)	46 (45)	
>2 n (%)	8 (8)	12 (12)	9 (9)	
Previous GDM (%)	45 (44)	33 (32)	24 (24)	**0.007**
Breastfeeding (months)	8.5 (4.7)	8.4 (4.9)	7.9 (5.9)	0.62
Total physical activity	8.3 (1.5)	8.3 (1.3)	7.9 (1.2)	0.09
Sport index	2.3 (0.9)	2.2 (0.7)	2.2 (0.7)	0.38
Leisure time index	3.1 (0.6)	3.1 (0.6)	3.0 (0.5)	0.19
Work index	2.8 (0.7)	3.0 (0.5)	2.8 (0.6)	0.07
BMI (kg/m^2)	24.9 (5.2)	25.6 (4.7)	26.4 (5.0)	0.10
Waist circumference (cm)	84.7 (11.8)	88.1 (12.6)	89.5 (12.4)	**0.016**
Total cholesterol (mmol/l)	4.7 (0.8)	4.7 (0.9)	4.6 (0.8)	0.60
LDL cholesterol (mmol/l)	2.8 (0.7)	2.7 (0.8)	2.7 (0.7)	0.88
HDL cholesterol (mmol/l)	1.5 (0.4)	1.5 (0.4)	1.4 (0.3)	**0.018**
Triglycerides (mmol/l)	0.8 (0.7–1.1)	0.9 (0.7–1.3)	0.9 (0.7–1.3)	0.06
CRP (mg/l)	0.9 (0.4–2.6)	1.0 (0.6–2.1)	1.6 (0.7–3.4)	**0.006**
Insulin sensitivity/resistance:				
Matsuda index	11.1 (7.4–15.4)	7.1 (4.9–11.1)	6.9 (4.3–11.5)	**<0.001**
HOMA-IR	0.9 (0.6–1.4)	1.4 (1.0–2.1)	1.6 (1.0–2.2)	**<0.001**
Beta-cell function:				
ISSI-2	598 (237)	744 (252)	912 (307)	**<0.001**
IGI/HOMA-IR	4.8 (2.6–7.5)	8.4 (6.2–12.6)	15.3 (10.6–25.3)	**<0.001**
OGTT:				
Fasting glucose (mmol/l)	4.9 (0.6)	4.8 (0.4)	4.6 (0.3)	**<0.001**
2-h glucose (mmol/l)	6.9 (2.0)	6.3 (1.5)	5.5 (1.3)	**<0.001**
CIR	0.2 (0.1–0.2)	0.4 (0.4–0.5)	0.9 (0.7–1.2)	**<0.001**
At 3-years				
Total physical activity	8.3 (1.7)	8.3 (1.6)	8.0 (1.3)	0.20
Sport index	2.7 (1.1)	2.7 (1.0)	2.5 (1.0)	0.37
Leisure time index	3.0 (0.6)	3.0 (0.5)	2.9 (0.5)	0.36
Work index	2.6 (0.7)	2.6 (0.7)	2.5 (0.6)	0.75
BMI (kg/m^2)	25.2 (5.5)	25.7 (4.9)	26.3 (4.8)	0.30
Waist circumference (cm)	85.9 (12.4)	88.4 (11.8)	89.4 (12.4)	0.11
Total cholesterol (mmol/l)	4.6 (0.8)	4.6 (0.9)	4.5 (0.9)	0.52
LDL cholesterol (mmol/l)	2.6 (0.7)	2.7 (0.8)	2.6 (0.7)	0.72
HDL cholesterol (mmol/l)	1.5 (0.4)	1.5 (0.3)	1.4 (0.3)	**0.038**
Triglycerides (mmol/l)	0.9 (0.7–1.1)	1.0 (0.7–1.3)	0.9 (0.7–1.3)	0.23
CRP (mg/l)	0.8 (0.3–1.8)	1.1 (0.5–2.0)	1.4 (0.5–3.3)	**0.032**
Insulin sensitivity/resistance:				
Matsuda index	8.7 (5.5–11.5)	6.9 (4.4–9.6)	7.1 (3.8–10.9)	0.07
HOMA-IR	1.2 (0.8–1.8)	1.4 (0.9–2.1)	1.5 (1.0–2.5)	**0.036**
Beta-cell function:				
ISSI-2	674 (276)	772 (270)	920 (403)	**<0.001**
IGI/HOMA-IR	6.2 (4.2–11.1)	9.4 (6.3–13.6)	13.2 (8.8–22.8)	**<0.001**

(Table 1 continues on next page)

	Lowest CIR tertile (0.01–0.30) (n = 102)	Middle CIR tertile (0.30–0.56) (n = 102)	Highest CIR tertile (0.56–10.95) (n = 102)	p
(Continued from previous page)				
OGTT:				
Fasting glucose (mmol/l)	4.9 (0.6)	4.7 (0.5)	4.5 (0.4)	**<0.001**
2-h glucose (mmol/l)	7.0 (2.1)	6.4 (1.8)	6.0 (1.5)	**<0.001**
Pre-diabetes/diabetes n (%)	29 (28)	24 (24)	11 (11)	**0.006**
Change in CIR from 1-year	0.1 (0.0–0.4)	0.0 (−0.1–0.2)	−0.2 (−0.4–0.2)	**<0.001**
CIR	0.3 (0.2–0.5)	0.5 (0.3–0.7)	0.8 (0.6–1.2)	**<0.001**
At 5-years				
Total physical activity	8.1 (1.6)	8.3 (1.6)	7.9 (1.4)	0.13
Sport index	2.7 (1.1)	2.8 (1.1)	2.6 (1.0)	0.21
Leisure time index	3.0 (0.6)	3.0 (0.6)	2.9 (0.6)	0.17
Work index	2.4 (0.7)	2.4 (0.6)	2.4 (0.6)	0.83
BMI (kg/m^2)	25.4 (5.3)	25.6 (4.8)	26.5 (4.7)	0.26
Waist circumference (cm)	87.3 (14.3)	87.6 (11.5)	89.7 (10.8)	0.33
Total cholesterol (mmol/l)	4.6 (0.8)	4.6 (0.7)	4.5 (0.8)	0.97
LDL cholesterol (mmol/l)	2.4 (0.7)	2.5 (0.7)	2.5 (0.7)	0.75
HDL cholesterol (mmol/l)	1.6 (0.4)	1.6 (0.3)	1.5 (0.4)	0.09
Triglycerides (mmol/l)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.0 (0.8–1.4)	0.71
CRP (mg/l)	1.0 (0.5–2.6)	0.8 (0.4–2.2)	1.3 (0.4–3.1)	0.14
Insulin sensitivity/resistance:				
Matsuda index	8.1 (4.9–11.4)	6.8 (4.4–10.7)	6.8 (4.1–9.4)	0.09
HOMA-IR	1.2 (0.8–1.9)	1.4 (0.9–2.0)	1.5 (1.1–2.2)	**0.018**
Beta-cell function:				
ISSI-2	646 (279)	711 (235)	937 (361)	**<0.001**
IGI/HOMA-IR	6.9 (4.5–10.2)	9.2 (5.9–12.5)	13.1 (8.2–18.9)	**<0.001**
OGTT:				
Fasting glucose (mmol/l)	4.9 (0.7)	4.7 (0.4)	4.6 (0.5)	**<0.001**
2-h glucose (mmol/l)	7.6 (2.7)	6.8 (1.5)	6.0 (1.7)	**<0.001**
Pre-diabetes/diabetes n (%)	36 (35)	25 (25)	12 (12)	**<0.001**
Change in CIR from 1-year	0.1 (0.0–0.3)	0.0 (−0.1–0.2)	−0.1 (−0.4–0.2)	**<0.001**
CIR	0.3 (0.2–0.5)	0.5 (0.3–0.6)	0.8 (0.5–1.1)	**<0.001**

Continuous data are presented as mean ± standard deviation (if normal distribution) or median followed by interquartile range in parentheses (if skewed distribution). Categorical variables are presented as absolute number followed by percentage in parentheses. Bold indicates p < 0.05.

Table 1: **Clinical and cardiometabolic characteristics at 1-year, 3-years and 5-years postpartum in study population, stratified into tertiles of corrected insulin response (CIR) at 1-year.**

performed with further adjustment for history of GDM and for physical activity in the preceding year and duration of breastfeeding. Logistic regression analyses of pre-diabetes or diabetes at 3-years and 5-years were performed with age, ethnicity, family history of diabetes, BMI at 1-year postpartum, and baseline CIR tertiles, respectively (Fig. 2). All analyses were conducted using R 4.2.2.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 23, 2003 and March 31, 2014, 306 women were enrolled. Table 1 shows the clinical and cardiometabolic characteristics of the study population stratified according to tertiles of CIR at 1-year postpartum. There were no differences between the lowest, middle and highest CIR tertiles in age, ethnicity, family history of diabetes or parity, though the prevalence of previous GDM was lowest in the highest tertile (p = 0.007).

At 1-year, there was a progressive increase in waist circumference from the lowest to middle to highest CIR tertile (p = 0.016), with no significant differences in BMI, physical activity or duration of breastfeeding. Similarly, CRP progressively increased across the tertiles (p = 0.006), mirrored by decreasing HDL (p = 0.018), with no other differences in lipid measures. Consistent with these findings, there was also a pattern of worsening insulin sensitivity/resistance across the CIR tertiles (Matsuda index p < 0.001; HOMA-IR p < 0.001). Conversely, however, there was a stepwise improvement in beta-cell function from the lowest to

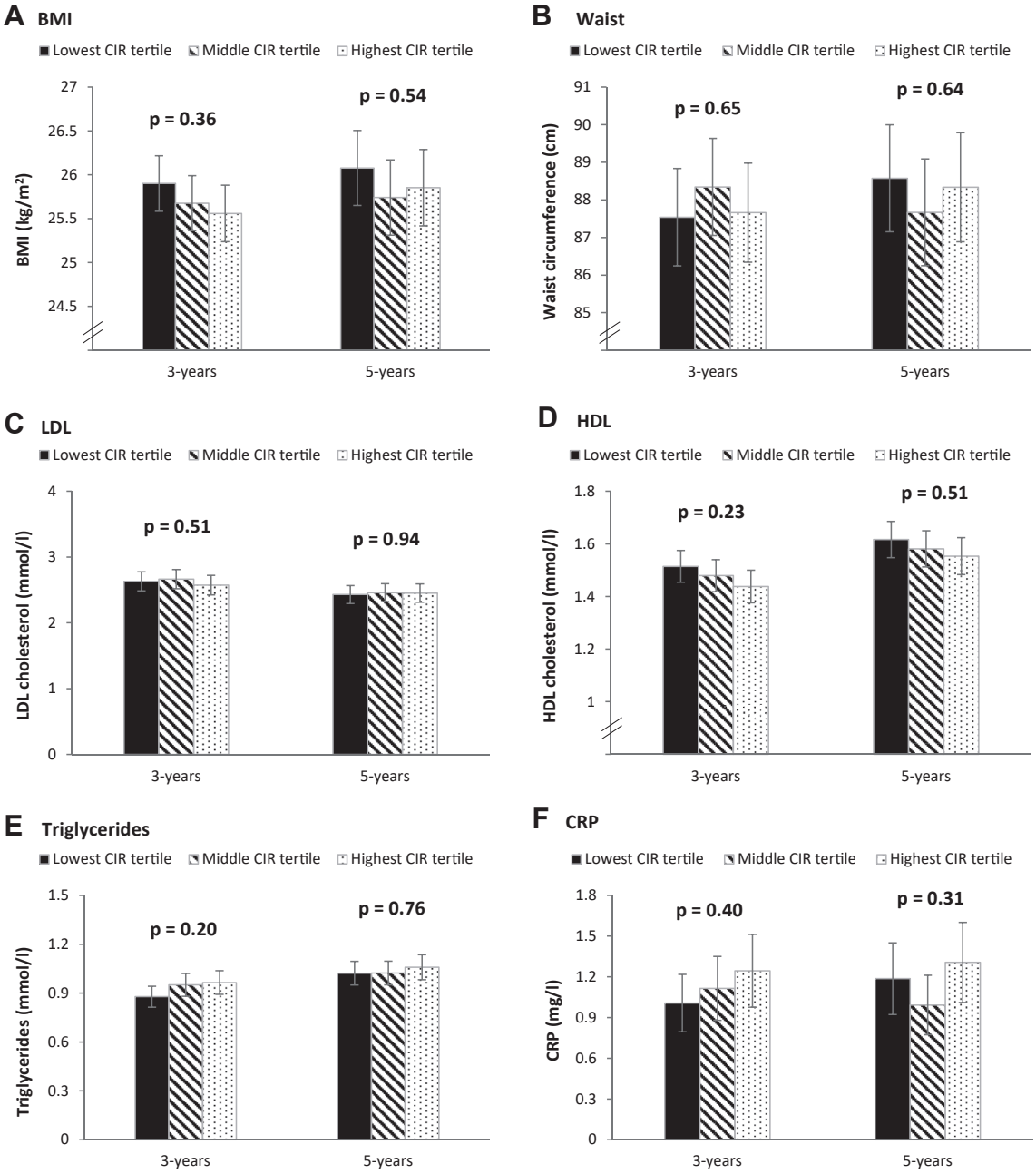

Fig. 1: Mean adjusted levels of cardiometabolic risk factors at 3-years and 5-years, respectively, in relation to CIR tertiles at 1-year postpartum. All risk factors adjusted for age, ethnicity, family history of DM, parity, BMI at 1-year, duration of breastfeeding, and time since delivery.

middle to highest CIR tertile (ISSI-2 $p < 0.001$; IGI/HOMA-IR $p < 0.001$), which was mirrored by decreasing fasting ($p < 0.001$) and 2-h glucose ($p < 0.001$). Thus, these unadjusted cross-sectional analyses suggested that the highest CIR tertile exhibited cardiometabolic features that were both favourable (better beta-cell function, lower glycaemia) and unfavourable (higher waist, CRP, and insulin resistance, with lower HDL).

At 3-years, there was some attenuation of these unfavourable features, though the patterns of lower HDL ($p = 0.038$), higher CRP ($p = 0.032$) and higher HOMA-IR ($p = 0.036$) still reached statistical significance (Table 1). By contrast, the favourable features of better beta-cell function (ISSI-2 $p < 0.001$; IGI/HOMA-IR $p < 0.001$) and lesser glycaemia (fasting glucose $p < 0.001$; 2-h glucose $p < 0.001$) remained readily apparent. There was also a progressive decrease in the

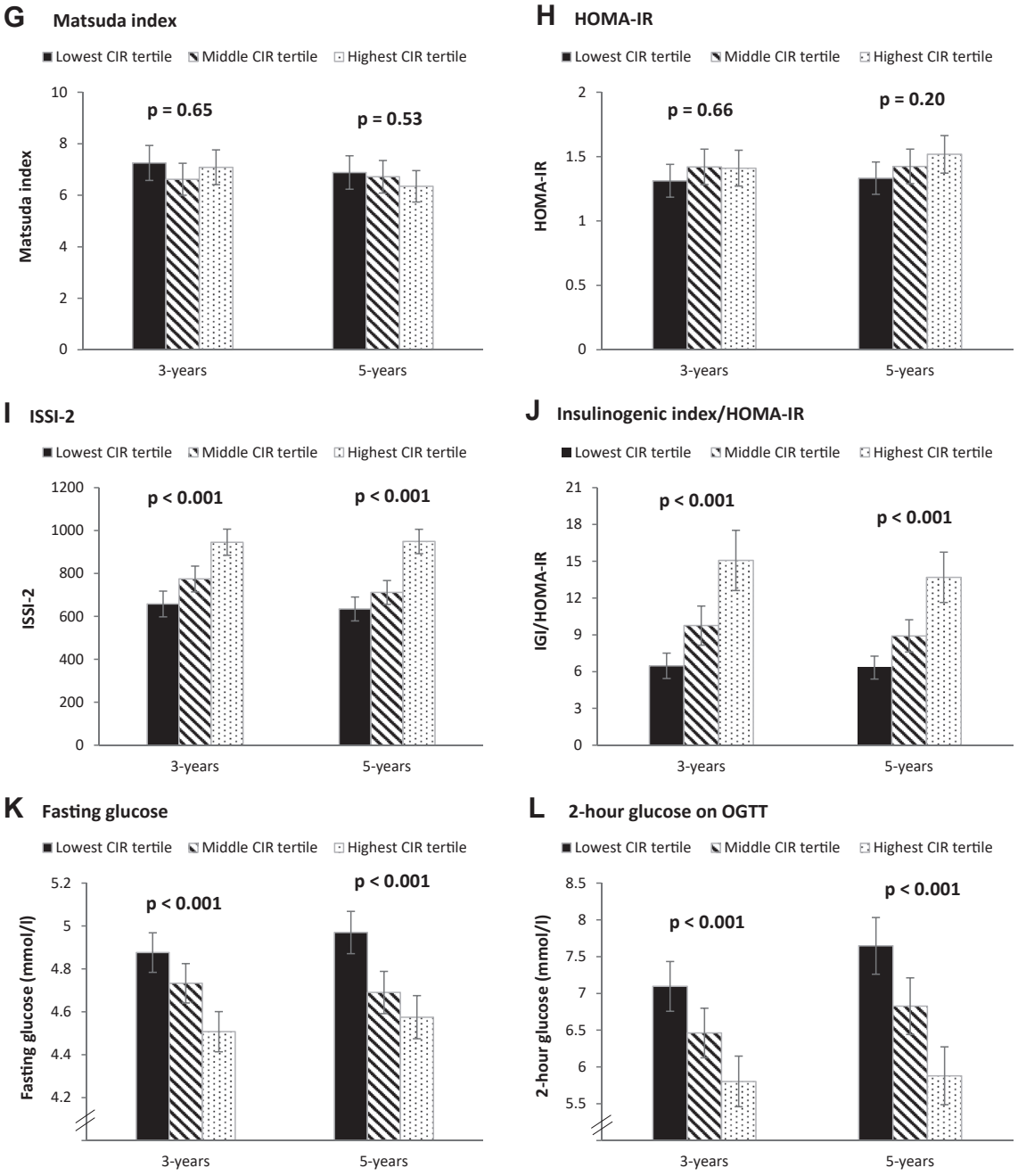

Fig. 1: Continued.

prevalence of pre-diabetes or diabetes (the vast majority of which was pre-diabetes) from the lowest to middle to highest CIR tertile ($p = 0.006$) At 5-years, the sole adverse element associated with higher baseline CIR was higher HOMA-IR ($p = 0.018$), whereas the desirable features of better beta-cell function (both $p < 0.001$), lower glycaemia (both $p < 0.001$) and less pre-diabetes or diabetes ($p < 0.001$) remained unchanged.

We next evaluated mean adjusted levels of cardiometabolic risk factors at 3- and 5-years in the 1-year CIR tertiles (Fig. 1). After adjustment for age, ethnicity, family history of diabetes, parity, baseline BMI, duration of breastfeeding and time since delivery, there were no significant differences between the CIR tertiles in BMI, waist, LDL, HDL, triglycerides, CRP, Matsuda index or HOMA-IR at either 3-years or 5-years

	Unadjusted model		p	Adjusted model		p
	β estimate	95% CI		β estimate	95% CI	
At 3-years						
BMI (kg/m^2)			0.38			0.23
Highest CIR tertile at 1-yr	0.99	(−0.41, 2.38)		−0.38	(−0.83, 0.07)	
Middle CIR tertile at 1-yr	0.40	(−0.99, 1.78)		−0.25	(−0.69, 0.19)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Waist circumference (cm)			0.11			0.59
Highest CIR tertile at 1-yr	3.51	(0.18, 6.83)		−0.78	(−2.35, 0.80)	
Middle CIR tertile at 1-yr	2.46	(−0.87, 5.79)		−0.14	(−1.70, 1.42)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
LDL cholesterol (mmol/l)			0.71			0.57
Highest CIR tertile at 1-yr	−0.02	(−0.22, 0.19)		−0.02	(−0.16, 0.13)	
Middle CIR tertile at 1-yr	0.07	(−0.14, 0.27)		0.06	(−0.08, 0.20)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
HDL cholesterol (mmol/l)			**0.03**			0.79
Highest CIR tertile at 1-yr	−0.13	(−0.22, −0.03)		−0.02	(−0.08, 0.04)	
Middle CIR tertile at 1-yr	−0.06	(−0.15, 0.04)		−0.003	(−0.06, 0.05)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log triglycerides (mmol/l)			0.11			0.88
Highest CIR tertile at 1-yr	0.11	(−0.003, 0.22)		0.02	(−0.06, 0.10)	
Middle CIR tertile at 1-yr	0.10	(−0.01, 0.21)		0.01	(−0.07, 0.10)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log CRP (mg/l)			0.06			0.88
Highest CIR tertile at 1-yr	0.41	(0.07, 0.74)		0.07	(−0.21, 0.34)	
Middle CIR tertile at 1-yr	0.18	(−0.15, 0.52)		0.05	(−0.22, 0.32)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log Matsuda index			0.15			0.48
Highest CIR tertile at 1-yr	−0.16	(−0.33, 0.01)		0.08	(−0.05, 0.20)	
Middle CIR tertile at 1-yr	−0.14	(−0.31, 0.03)		0.05	(−0.07, 0.18)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log HOMA-IR			0.07			0.90
Highest CIR tertile at 1-yr	0.20	(0.03, 0.37)		−0.03	(−0.17, 0.11)	
Middle CIR tertile at 1-yr	0.13	(−0.04, 0.30)		−0.03	(−0.16, 0.11)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log ISSI-2			**<0.001**			**0.02**
Highest CIR tertile at 1-yr	0.31	(0.20, 0.41)		0.16	(0.05, 0.27)	
Middle CIR tertile at 1-yr	0.14	(0.04, 0.25)		0.07	(−0.03, 0.17)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log IGI/HOMA-IR			**<0.001**			**<0.001**
Highest CIR tertile at 1-yr	0.73	(0.49, 0.96)		0.82	(0.49, 1.16)	
Middle CIR tertile at 1-yr	0.36	(0.12, 0.60)		0.42	(0.15, 0.69)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Fasting glucose (mmol/l)			**<0.001**			**<0.001**
Highest CIR tertile at 1-yr	−0.33	(−0.46, −0.19)		−0.23	(−0.34, −0.11)	
Middle CIR tertile at 1-yr	−0.11	(−0.25, 0.02)		−0.09	(−0.21, 0.02)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
2-h glucose (mmol/l)			**<0.001**			0.19
Highest CIR tertile at 1-yr	−1.01	(−1.50, −0.52)		−0.41	(−0.86, 0.03)	
Middle CIR tertile at 1-yr	−0.55	(−1.04, −0.05)		−0.24	(−0.66, 0.18)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	

(Table 2 continues on next page)

	Unadjusted model		p	Adjusted model		p
	β estimate	95% CI		β estimate	95% CI	
(Continued from previous page)						
At 5-years						
BMI (kg/m^2)			0.40			0.43
Highest CIR tertile at 1-yr	0.93	(−0.49, 2.35)		−0.29	(−0.89, 0.32)	
Middle CIR tertile at 1-yr	0.18	(−1.24, 1.59)		−0.38	(−0.98, 0.22)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Waist circumference (cm)			0.32			0.14
Highest CIR tertile at 1-yr	2.44	(−0.92, 5.79)		−1.43	(−3.33, 0.46)	
Middle CIR tertile at 1-yr	0.41	(−2.94, 3.77)		−1.82	(−3.69, 0.06)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
LDL cholesterol (mmol/l)			0.72			0.53
Highest CIR tertile at 1-yr	0.07	(−0.12, 0.27)		0.08	(−0.06, 0.22)	
Middle CIR tertile at 1-yr	0.07	(−0.13, 0.26)		0.05	(−0.09, 0.19)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
HDL cholesterol (mmol/l)			0.08			0.94
Highest CIR tertile at 1-yr	−0.12	(−0.22, −0.01)		−0.003	(−0.07, 0.07)	
Middle CIR tertile at 1-yr	−0.06	(−0.16, 0.05)		−0.01	(−0.08, 0.06)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log triglycerides (mmol/l)			0.64			0.57
Highest CIR tertile at 1-yr	0.05	(−0.05, 0.16)		−0.01	(−0.10, 0.07)	
Middle CIR tertile at 1-yr	0.02	(−0.08, 0.12)		−0.04	(−0.13, 0.04)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log CRP (mg/l)			0.11			0.24
Highest CIR tertile at 1-yr	0.23	(−0.11, 0.57)		−0.13	(−0.41, 0.15)	
Middle CIR tertile at 1-yr	−0.13	(−0.46, 0.21)		−0.24	(−0.51, 0.04)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log Matsuda index			0.11			0.12
Highest CIR tertile at 1-yr	−0.18	(−0.34, −0.01)		0.02	(−0.11, 0.15)	
Middle CIR tertile at 1-yr	−0.07	(−0.24, 0.09)		0.12	(−0.004, 0.25)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log HOMA-IR			**0.02**			0.49
Highest CIR tertile at 1-yr	0.23	(0.07, 0.40)		0.05	(−0.09, 0.18)	
Middle CIR tertile at 1-yr	0.12	(−0.04, 0.29)		−0.03	(−0.16, 0.10)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log ISSI-2			**<0.001**			**0.002**
Highest CIR tertile at 1-yr	0.39	(0.28, 0.50)		0.19	(0.08, 0.31)	
Middle CIR tertile at 1-yr	0.13	(0.01, 0.24)		0.03	(−0.07, 0.13)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Log IGI/HOMA-IR			**<0.001**			**<0.001**
Highest CIR tertile at 1-yr	0.66	(0.43, 0.88)		0.67	(0.36, 0.99)	
Middle CIR tertile at 1-yr	0.27	(0.05, 0.50)		0.33	(0.08, 0.58)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
Fasting glucose (mmol/l)			**<0.001**			**<0.001**
Highest CIR tertile at 1-yr	−0.34	(−0.48, −0.19)		−0.19	(−0.30, −0.07)	
Middle CIR tertile at 1-yr	−0.24	(−0.39, −0.10)		−0.21	(−0.32, −0.10)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	
2-h glucose (mmol/l)			**<0.001**			**0.008**
Highest CIR tertile at 1-yr	−1.63	(−2.18, −1.08)		−0.82	(−1.33, −0.31)	
Middle CIR tertile at 1-yr	−0.76	(−1.31, −0.21)		−0.40	(−0.88, 0.08)	
Lowest CIR tertile at 1-yr	*Ref*	*Ref*		*Ref*	*Ref*	

The p-values reflect the overall significance of CIR tertiles at 1-year in predicting the indicated cardiometabolic risk factor at 3-years or 5-years, respectively, in the indicated models. Bold indicates p < 0.05.

Table 2: **Associations of CIR tertiles at 1-year with cardiometabolic risk factors at 3-yrs and 5-yrs, respectively, before (unadjusted model) and after adjustment for age, ethnicity, family history of diabetes, BMI at 1-year, and baseline (1-year) measure of the respective risk factor (adjusted model).**

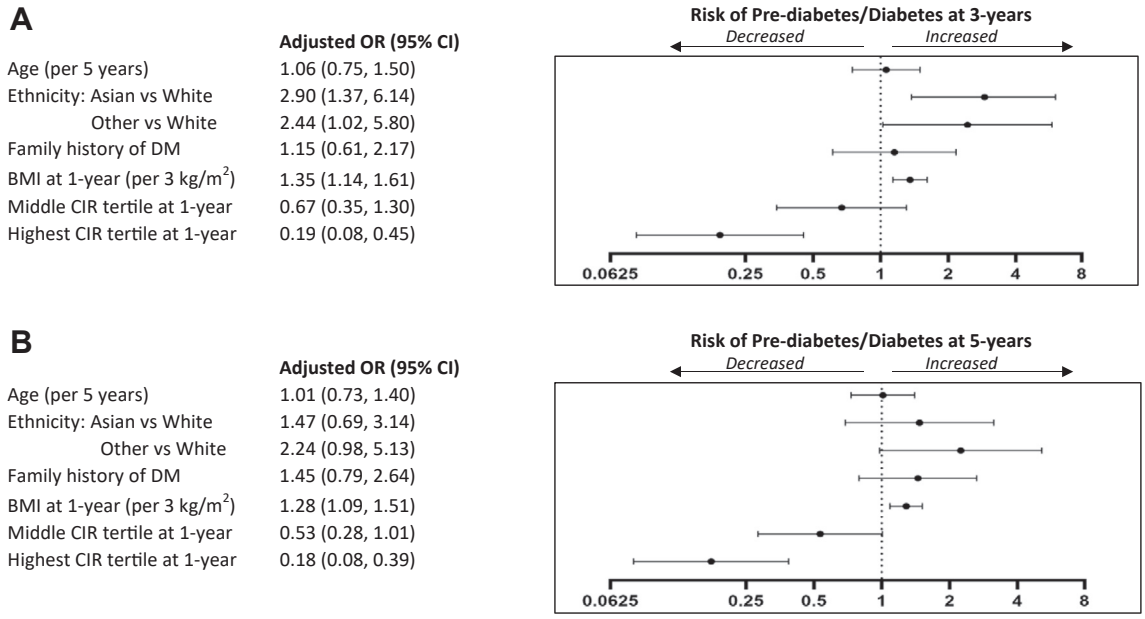

Fig. 2: Logistic regression analyses of pre-diabetes or diabetes at (A) 3-years and (B) 5-years, respectively.

(Panel A–H). By contrast, at both 3- and 5-years, there was stepwise increase in mean adjusted ISSI-2 and IGI/HOMA-IR from the lowest to middle to highest CIR tertile (all $p < 0.001$) (Panels I and J). Moreover, these findings were mirrored by a progressive decrease in mean adjusted fasting and 2-h glucose (all $p < 0.001$) (Panels K and L). All of these findings were unchanged on sensitivity analyses that were further adjusted for history of GDM (data not shown). Thus, on longitudinal analyses adjusted for covariates, higher CIR at 1-year was independently associated with better beta-cell function and lower glycaemia at 3-years and 5-years.

We next evaluated baseline CIR tertiles at 1-year as predictors of unadjusted and adjusted cardiometabolic risk factors at 3-years and 5-years, respectively (Table 2). Upon adjustment for clinical risk factors for diabetes (age, ethnicity, family history of diabetes, baseline BMI) and the baseline measure of the respective risk factor, CIR tertile at 1-year was not a significant predictor of the ensuing adjusted BMI, waist, LDL, HDL, triglycerides, CRP, Matsuda index or HOMA-IR. However, CIR tertile at 1-year was independently associated with ISSI-2 at 3-years ($p = 0.02$) and 5-years ($p = 0.002$), with the highest CIR tertile predicting higher adjusted ISSI-2 compared to the lowest tertile at both points in time. Similarly, baseline CIR tertile was independently associated with IGI/HOMA-IR at 3- and 5-years (both $p < 0.001$), with the highest and middle tertiles emerging as positive independent predictors. Moreover, baseline CIR tertile was independently associated with fasting glucose at 3-years and 5-years (both $p < 0.001$), with the highest tertile predicting lower adjusted fasting glucose compared to the lowest tertile at both timepoints. Baseline CIR tertile did not reach significance in its association with adjusted 2-h glucose at 3-years ($p = 0.19$) but did so at 5-years ($p = 0.008$), with the highest tertile again emerging as a significant predictor of lower adjusted 2-h glucose, as compared to the lowest tertile. All of these findings were unchanged on sensitivity analyses with further adjustment for physical activity in the preceding year and duration of breastfeeding (data not shown) and history of GDM (data not shown).

Finally, we constructed logistic regression models of (dependent variable) pre-diabetes or diabetes at 3- and 5-years, with covariates consisting of clinical risk factors for diabetes (age, ethnicity, family history of diabetes, and baseline BMI at 1-year) and baseline CIR tertiles. On these analyses, the highest CIR tertile at 1-year predicted lower risk of pre-diabetes or diabetes at both 3-years (adjusted OR = 0.19; 95% CI 0.08–0.45) (Fig. 2A) and 5-years (aOR = 0.18; 0.08–0.39) (Fig. 2B). These findings were unchanged on sensitivity analyses further adjusted for physical activity in the preceding year and duration of breastfeeding (data not shown). Moreover, on sensitivity analyses restricted to women with normal glucose tolerance at baseline, the highest CIR tertile at 1-year continued to predict lower risk of incident pre-diabetes or diabetes at both 3-years (adjusted OR = 0.28; 95% CI 0.09–0.83) and 5-years (adjusted OR = 0.19; 0.07–0.49) (data not shown). Thus, a robust insulin secretory response at 1-year predicted not only better beta-cell function and lower glycaemia in the ensuing 4 years but also a lower risk of pre-diabetes or diabetes.

Discussion

In this study, we demonstrate 3 main findings. First, on cross-sectional analyses at baseline, higher CIR was associated with both adverse (greater waist circumference, higher CRP, lower HDL cholesterol, greater insulin resistance) and favourable (better beta-cell function, lower glycemia) cardiometabolic features. However, adjusted longitudinal analyses revealed only beneficial future implications. Notably, higher CIR tertile at baseline was independently associated with (i) better beta-cell compensation (ISSI-2 and IGI/HOMA-IR) and (ii) lower glycaemia (fasting and 2-h glucose) at both 3-years and 5-years, but exhibited no significant associations with BMI, waist, lipids, CRP or insulin resistance. Third, on logistic regression analyses, the highest CIR tertile at baseline emerged as a significant independent predictor of lower future risk of prediabetes or diabetes, as evident at both 3-years and 5-years. It thus emerges that a brisk post–challenge insulinemic response is not an indicator of adverse cardiometabolic health but, rather, portends favourable metabolic function in the years to come.

The physiologic relevance of postprandial hyperinsulinemia stands at the crux of two ongoing debates in the literature.[1–8] One debate pertains to the etiology of obesity, which is generally attributed to a disequilibrium between higher caloric intake and reduced energy expenditure, resulting in positive energy balance and enhanced adipose tissue deposition.[32] By contrast, the alternative carbohydrate-insulin model posits that postprandial hyperinsulinemia in response to a high glycemic load can induce an anabolic state that promotes weight gain and thereby leads to obesity.[8] Postprandial insulin secretion has also been implicated in a second debate pertaining to the early natural history of T2DM. Specifically, some investigators have suggested that insulin hypersecretion may be a pathogenic feature that contributes to the development of dysglycaemia, in contrast to the more conventional view wherein beta-cell dysfunction is the primary pathophysiologic event.[2–4] With both of these questions, the role of postprandial insulin hypersecretion has remained controversial because of conflicting findings that may be partly attributed to certain limitations that are pervasive across this literature.

One such limitation is variation between studies in considering the impact of glucose on post–challenge insulin secretion. Notably, many studies have assessed postprandial insulinemia without accounting for differences in baseline glycaemia. As recently demonstrated by Esser, Utzschneider and Kahn,[4] isolated interpretation of insulinemia without consideration of its glycaemic stimulus may yield misleading conclusions about the appropriateness of the secretory response and beta-cell function. It was for this reason that CIR was first derived as a reproducible measure of the insulin secretory response to the OGTT that is independent of ambient glycaemia.[11] Indeed, its relevance to the current context was recently demonstrated with dueling Mendelian randomisation studies wherein insulinemia at 30-min post–challenge was implicated as metabolically deleterious whereas higher CIR was identified as potentially beneficial.[9,10]

A second limitation plaguing this literature is that most studies have been cross-sectional. Moreover, the few longitudinal studies evaluating post–challenge insulin secretion have generally not accounted for the impact of glucose and have yielded mixed findings. For example, in a study of 107 adult offspring of parents who both had T2DM, those with a comparatively higher first-phase insulin response to intravenous glucose at baseline exhibited greater weight gain over time,[33] potentially implicating post–challenge hyperinsulinemia as a causative factor (though it should be recognised that the participants all had a genetic predisposition to T2DM through both parents). By contrast, in a study of 591 children with obesity, Halloun et al. recently reported no association between the insulin secretory response on the OGTT and changes in the degree of obesity over subsequent mean follow-up of 1.86 years, arguing against the carbohydrate-insulin model.[6] Taken together, these limitations suggest a need for longitudinal study in which the cardiometabolic implications of the glucose-corrected post–challenge insulin secretory response have been followed over time.

The current study was designed to address this need through 3 features. First, in reflecting the complete spectrum of glucose tolerance in pregnancy, the 306 participants represent a broad range of future risk of T2DM and cardiovascular disease,[14–17] and hence a relevant population in which to study determinants of cardiometabolic risk. Second, the measurement of baseline CIR enabled assessment of their post–challenge insulinemic response independent of glycaemia. Third, participants underwent systematic characterisation on 3 occasions over 4-years, thereby enabling serial evaluation of their cardiometabolic risk factors over time in relation to baseline CIR. With this approach, we found that unadjusted cross-sectional analyses at baseline yielded associations of CIR with both adverse and favourable cardiometabolic features. However, adjusted longitudinal analyses revealed consistent independent associations of higher CIR with better beta-cell function, lower glycaemia and lower risk of prediabetes or diabetes in the years thereafter. In the context of the ongoing etiologic debates noted above,[1–8] these data argue against the concept of post–challenge hyperinsulinemia being a pathologic response that holds adverse cardiometabolic consequences for the future.

Our findings are consistent with previous reports suggesting beneficial effects of higher CIR.[10,34] Most notably, in the Diabetes Prevention Program, higher

CIR was associated with a lower risk of progression to diabetes in individuals with pre-diabetes at baseline.[34] The current report extends these observations to a much earlier point in the natural history of diabetes by showing that higher CIR is similarly associated with a lower risk of progression to dysglycaemia (primarily pre-diabetes) in young women. Accordingly, the current demonstration enhances the argument against post-prandial insulinemia being a pathologic factor in the context of the aforementioned debates pertaining to the early etiologies of obesity and diabetes.

A limitation of this study is the absence of dietary assessment of the participants such that the possibility of effect modification by diet could not be assessed. Of note, an earlier study of 276 adults reported that serum insulin at 30-min on the OGTT (without consideration of glucose) was associated with weight gain amongst those in the lowest tertile of dietary fat, with no such association observed in the highest tertile.[35] Another limitation to recognise is that the peripheral insulin concentration cannot be interpreted as a measure of pancreatic insulin secretion, owing to the fact that this concentration is also influenced by hepatic insulin clearance (and hence reflects the balance between secretion and clearance). Indeed, the technique of C-peptide deconvolution is needed to calculate pre-hepatic insulin secretion[36] but such assessment was not possible in this study owing to the absence of C-peptide measurements. Similarly, clamp studies would have provided direct assessment of insulin sensitivity/resistance and beta-cell function (in contrast to the OGTT-based surrogate indices reported herein). Conversely, it should be noted that the OGTT enabled concurrent assessment of glucose tolerance and was more amenable to serial assessment on 3 occasions over 4 years than would be more invasive and demanding clamp studies. Moreover, the OGTT-based measures in this study are all established and validated indices that have been widely implemented in previous studies.[18–28]

These findings hold clinical implications in the context of current debate around the interpretation and implications of postprandial insulinemia. Specifically, practitioners who believe that postprandial hyperinsulinemia is metabolically deleterious may make clinical recommendations that seek to limit insulinemic excursion after meals. In providing evidence that post–challenge insulinemia does not hold adverse cardiometabolic implications, the current findings argue against clinical recommendations that focus on limiting the postprandial insulin secretory response for purported metabolic benefit.

In summary, this prospective cohort study shows that, on unadjusted cross-sectional analyses, higher CIR has associations with both adverse and favourable cardiometabolic features. However, adjusted longitudinal analyses reveal only beneficial future implications, with higher baseline CIR independently associated with better beta-cell function and lower glycaemia at both 2-years and 4-years thereafter. Moreover, higher CIR at baseline is a significant independent predictor of lower future risk of pre-diabetes or diabetes. Thus, a robust post–challenge insulin secretory response does not indicate adverse cardiometabolic health but, rather, predicts favourable metabolic function in the years to come.

Contributors

RR, AJH, PWC, MS, and BZ designed and implemented the study. JP performed the statistical analyses. RR wrote the manuscript. RR and JP accessed and verified the data. RR is guarantor, had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility to submit for publication. All authors critically revised the manuscript for important intellectual content. All authors approved the final manuscript and its submission.

Data sharing statement

De-identified data can be made available under restricted access from the corresponding author (Ravi.Retnakaran@SinaiHealth.ca), for academic purposes, subject to a material transfer agreement and approval of the Mount Sinai Hospital Research Ethics Board. Individual participant data that underlie the results reported in this article can be made available by this mechanism, after de-identification, to achieve the aims in the approved proposal. Access is controlled in this way because of the clinical nature of the data. The study protocol can also be made available in this way. This data access mechanism will be available beginning 9 months and ending 36 months following publication of this article.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102363.

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